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Copper-mediated direct arylation of benzoazoles with aryl iodides

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Abstract

The direct arylation of 1,3-benzoazole compounds with aryl iodides is effectively promoted by CuI with use of PPh_3 and Na_2CO_3 or K_3PO_4 as ligand and base, respectively, in DMF or DMSO to produce the corresponding 2-arylated products with good yields.

Keywords: Arylation; Aryl iodides; Benzoazoles; Copper

Various aryl-substituted azole compounds having imidazole, oxazole, and thiazole skeletons are known to exhibit pharmacological activities and also of importance in the area of π-conjugated functional materials. Among the most useful methods to prepare such arylheterocycles is the palladium-catalyzed cross-coupling of either heteroaryl halides with arylmetals or aryl halides with heteroarylmetals.[1] Meanwhile, it is known that aryl halides can couple directly with azoles as well as thiophenes and furans at their 2- and/or 5-position(s) in the presence of a palladium- or rhodium-based catalyst. The direct method has a significant advantage, not requiring stoichiometric pre-metalation of the heterocycles, and thus, has been studied extensively in recent years.[2]

In our previous work, we found that addition of a copper(I) species, typically CuI, can effectively enhance the above palladium-catalyzed direct arylation in some cases.[3a] It was also observed that the reaction of azoles with aryl iodides can proceed to some extent at the 2-position selectively by using the much less expensive copper species alone as a promoter. The copper-mediated method has been applied to the synthesis of 2-arylated imidazoles including combretastatin A-4 analogues[4] and COX-2 inhibitors[5] with moderate efficiency. As part of our study of the direct arylation of heteroarenes,[3] we have revisited the copper-mediated coupling for elaborating the reaction conditions. It has been found that the reaction of 1,3-benzoazoles is effectively promoted by CuI with use of PPh_3 and Na_2CO_3 or K_3PO_4 as ligand and base, respectively, in DMF or DMSO to produce the corresponding 2-arylated products with good yields. During the performance of this work, Do and Dougulis reported an effective copper-based catalytic system for the reaction with a strong base such as *t*-BuOLi, while excess aryl iodide (3 equiv) is usually required.[6] Their report prompted us to disclose our own results. The present protocol with the mild bases is conducted by using a nearly equimolar amount of aryl iodide as well as CuI, and thus, seems to be especially useful when an aryl iodide is relatively valuable.

The arylation of benzoxazole (**1**) (1 mmol) with iodobenzene (**2a**) (2 equiv) was first examined in the presence of CuI (0.1 equiv) and PPh_3 (0.2 equiv) by using a number of inorganic bases (2 mmol) in DMF (5 mL) at 160 °C for 8 h (Table 1, entries 1–4). Among the bases tested, K_3PO_4 was found to be the most effective one under the conditions employed to afford 2-phenylbenzoxazole (**3a**) in 87% yield. The yield of **3a** was apparently decreased without the addition of PPh_3 (entry 5). Decreasing the amount of iodobenzene to 1.2 equiv resulted in a poor yield of **3a** due to the formation of a byproduct in a significant amount (entry

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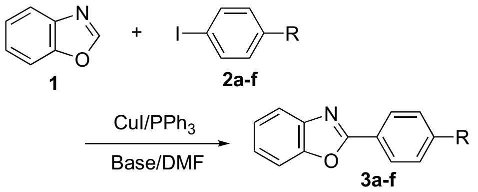
Table 1
Reaction of benzoxazole (**1**) with aryl iodides (**2**)



Entry	**2**, R	Base	Conditions[a]	**3**, % Yield[b]
1	**2a**, H	Na_2CO_3	A	**3a**, 37
2	**2a**, H	K_2CO_3	A	**3a**, 46
3	**2a**, H	Na_3PO_4	A	**3a**, 10
4	**2a**, H	K_3PO_4	A	**3a**, 87
5[c]	**2a**, H	K_3PO_4	A	**3a**, 37
6[d]	**2a**, H	K_3PO_4	A	**3a**, 8
7	**2a**, H	K_3PO_4	B	**3a**, 67
8	**2a**, H	Na_2CO_3	B	**3a**, 75 (70)
9	**2a**, H	Na_2CO_3	C	**3a**, 86 (82)
10[c]	**2a**, H	Na_2CO_3	C	**3a**, 26
11	**2b**, OMe	Na_2CO_3	C	**3b**, 78 (71)
12	**2c**, Cl	Na_2CO_3	C	**3c**, 90 (88)
13	**2d**, Br	Na_2CO_3	C	**3d**, (53)
14	**2e**, CO_2Me	Na_2CO_3	C	**3e**, (43)
15	**2f**, CN	Na_2CO_3	C	**3f**, (93)

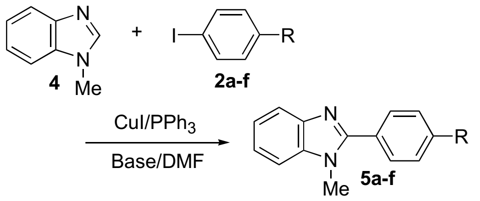
[a] (A) [**1**]:[**2**]:[CuI]:[PPh_3]:[Base] = 1:2:0.1:0.2:2 (in mmol), in DMF (5 mL) under N_2 at 160 °C for 8 h. (B) [**1**]:[**2**]:[CuI]:[PPh_3]:[Base] = 1:1.2:1:0.2:2 (in mmol), in DMF (5 mL) under N_2 at 160 °C for 8 h. (C) [**1**]:[**2**]:[CuI]:[PPh_3]:[Base] = 1:1.2:1:0.2:2 (in mmol), in DMF (1 mL) under N_2 at 160 °C for 2 h.

[b] GC yield. Value in parentheses indicates isolated yield.

[c] Reaction without PPh_3.

[d] [**2a**] = 1.2 mmol.

Table 2
Reaction of 1-methyl-1*H*-benzimidazole (**4**) with aryl iodides (**2**)



Entry	**2**, R	Base	Conditions[a]	**5**, % Yield[b]
1	**2b**, OMe	Na_2CO_3	A	**5b**, 84 (82)
2	**2b**, OMe	K_2CO_3	A	**5b**, 46
3	**2b**, OMe	Cs_2CO_3	A	**5b**, 10
4	**2b**, OMe	K_3PO_4	A	**5b**, 53
5[c]	**2b**, OMe	Na_2CO_3	A	**5b**, 49
6[d]	**2b**, OMe	Na_2CO_3	A	**5b**, 15
7[e]	**2b**, OMe	Na_2CO_3	A	**5b**, 42
8	**2b**, OMe	Na_2CO_3	B	**5b**, 81
9[f]	**2b**, OMe	Na_2CO_3	B	**5b**, 19
10	**2a**, H	Na_2CO_3	B	**5a**, (75)
11	**2c**, Cl	Na_2CO_3	B	**5c**, (89)
12	**2d**, Br	Na_2CO_3	B	**5d**, (60)
13	**2e**, CO_2Me	Na_2CO_3	B	**5e**, (52)
14	**2f**, CN	Na_2CO_3	B	**5f**, (69)

[a] (A) [**4**]:[**2**]:[CuI]:[PPh_3]:[Base] = 1:2:1:0.2:2 (in mmol), in DMF (5 mL) under N_2 at 160 °C for 8 h. (B) [**4**]:[**2**]:[CuI]:[PPh_3]:[Base] = 1:1.2:1:0.2:2 (in mmol), in DMF (5 mL) under N_2 at 160 °C for 8 h.

[b] GC yield. Value in parentheses indicates isolated yield.

[c] [PPh_3] = 1 mmol.

[d] Reaction without PPh_3.

[e] [CuI] = 0.5 mmol.

[f] Reaction in DMF (1 mL).

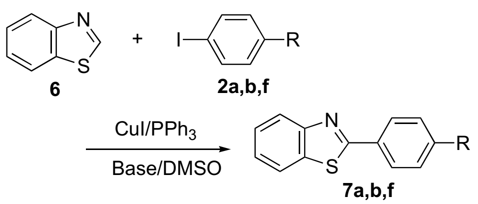
6, vide infra). When an equimolar amount of CuI was used, the yield of **3a** was increased even by using 1.2 equiv of **2a**, and the weaker base Na_2CO_3 was superior to K_3PO_4 under these conditions (entry 8 vs 7). Furthermore, the rate of the reaction was increased, when the reaction was carried out in a concentrated mixture using 1 mL of DMF (entry 9) to afford **3a** in 86% yield within 2 h. Removal of PPh_3 from these conditions also reduced the yield of **3a** (entry 10). Under the conditions employed for entry 9, various 4-substituted aryl iodides **2b**–**2f** having electron-donating and -withdrawing substituents gave the corresponding 2-arylbenzoxazoles **3b**–**f** with fair to excellent yields (entries 11–15). Thus, bromo, ester, and nitrile functions are tolerable in the present system.

Next, we examined the arylation of 1-methyl-1*H*-benzimidazole (**4**) as a typical imidazole substrate. The results for the reaction of **4** (1 mmol) with **2b** (2 equiv) in the presence of CuI (1 equiv) and PPh_3 (0.2 equiv) using a number of bases (2 equiv) in DMF (5 mL) at 160 °C for 8 h are shown in entries 1–4 of Table 2. In this reaction, Na_2CO_3 was also the base of choice and the arylated product **5b** was obtained in 84% yield (entry 1). The use of Cs_2CO_3 was, however, effective in the presence of 2 equiv of CuI as reported previously (73% for **5b**).[3a] The reaction either with 1 equiv of PPh_3 or without the ligand was less effective (entries 5 and 6). When the amount of CuI was reduced to 0.5 equiv, the yield of **5b** was also decreased (entry 7). On the other hand, decreasing the amount of **2b** to 1.2 equiv only little affected the reaction to afford a satisfactory yield of **5b** (entry 8). Unlike the reaction of benzoxazole, decreasing the amount of the solvent was not effective (entry 9). Using the conditions of entry 8, the reactions of **4** with **2a** and **2c**–**f** gave the corresponding 2-arylated products **5a** and **5c**–**f** with substantial yields (entries 10–14).

The arylation of benzothiazole (**6**) was also conducted. The effective conditions for the reaction of benzoxazole (**1**) were found to be not suitable in this case. The reaction of **6** (1 mmol) with **2a** (2 equiv) in the presence of CuI (1 equiv), PPh_3 (0.2 equiv), and Na_2CO_3 (2 equiv) in DMF (1 mL) for 2 h gave 2-phenylbenzothiazole (**7a**) in 34% yield (Table 3, entry 1). A good yield of **7a** was obtained in the reaction with 1.2 equiv of **2a** by using K_3PO_4 and DMSO as base and solvent, respectively (entry 4). Under the same conditions, iodides **2b** and **2f** reacted with **6** smoothly to afford **7b** and **7f** (entries 5 and 6).

As described above, the effective set of reaction conditions for each benzoazole is not unity, while each substrate can be arylated with an almost stoichiometric amount of aryl iodides. One of the major factors determining their reactivity may be the acidity of hydrogen at C-2. The order of acidity follows the sequence: **1** (benzoxazole) > **6** (benzo-

Table 3
Reaction of benzothiazole (**6**) with aryl iodides (**2**)



Entry	**2**, R	Base	Conditions[a]	**7**, % Yield[b]
1[c]	**2a**, H	Na_2CO_3	A	**7a**, 34
2	**2a**, H	Na_2CO_3	A	**7a**, 50
3	**2a**, H	K_3PO_4	A	**7a**, 74
4	**2a**, H	K_3PO_4	B	**7a**, 71 (63)
5	**2b**, OMe	K_3PO_4	B	**7b**, (78)
6	**2f**, CN	K_3PO_4	B	**7f**, (83)

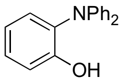
[a] (A) [**1**]:[**2**]:[CuI]:[PPh_3]:[Base] = 1:2:1:0.2:2 (in mmol), in DMSO (1 mL) under N_2 at 160 °C for 2 h. (B) [**1**]:[**2**]:[CuI]:[PPh_3]:[Base] = 1:1.2:1:0.2:2 (in mmol), in DMSO (1 mL) under N_2 at 160 °C for 2 h.

[b] GC yield. Value in parentheses indicates isolated yield.

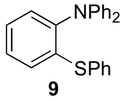
[c] Reaction in DMF (1 mL).

thiazole) > **4** (benzimidazole).[7] It may be reasonable to consider that the arylation proceeds via the initial cupration of C-2 accompanied by deprotonation in the presence of a base and the reaction of the resulting benzoazolylcopper(I) intermediate with an aryl iodide leads to the corresponding 2-arylbenzoazole.[5a]

It should be noted that in the reaction of **1** with **2a**, the formation of *o*-(diphenylamino)phenol (**8**) as byproduct was detected in each case and the amount of **8** depended on the reaction conditions. It was especially significant when the yield of **3a** was low by using a catalytic amount of CuI (for example, ca. 50% in entry 6 of Table 1). This seems to be due to the fact that the C-2 hydrogen of **1** is relatively more acidic and its anion readily undergoes ring-opening.[8] Then *o*-aminophenol formed by the successive hydrolysis may be diphenylated with **2a** in the reaction medium to give **8**.[9] Thus, an enough amount of either an aryl iodide or CuI seems to be required for an effective coupling. In the reaction of **6**, the formation of diphenyl-[2-(phenylthio)phenyl]amine (**9**) was identified, indicating that the sulfur undergoes phenylation under the conditions (for example, ca. 6% in entry 2 of Table 3). Such a byproduct was, however, not detected in the reaction of **4**, which may be attributed to the fact that the ring-opening is less favorable than the corresponding oxazole and thiazole.[8b]



8



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In summary, we have shown some effective protocols for the copper-mediated arylation of benzoazoles using less expensive, mild inorganic bases without the aid of a palladium catalyst.[10] The amount of aryl iodide required could be reduced to a nearly equimolar equivalent to the azoles. Work is underway toward further development of the direct method.

Acknowledgments

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9. Forest, J. *J. Chem. Soc.* **1960**, 581; *Compound* **8**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.51 (s, 1H), 6.88–6.92 (m, 1H), 6.97–7.03 (m, 7H), 7.06–7.09 (m, 1H), 7.15–7.17 (m, 1H), 7.19–7.25 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.4, 121.4, 121.7, 122.6, 127.6, 128.9, 129.3, 133.0, 146.6, 152.2. MS, *m*/*z* 261 (M^+). *Compound* **9**: ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (t, $J = 8.0$ Hz, 2H), 7.01 (d, $J = 8.0$ Hz, 4H), 7.04–7.09 (m, 2H), 7.13–7.17 (m, 2H), 7.22 (t, $J = 8.0$ Hz, 4H), 7.26–7.31 (m, 3H), 7.34–7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.8, 121.9, 126.4, 127.2, 127.8, 128.9, 129.1, 130.1, 130.8, 133.4, 134.0, 137.5, 144.6, 147.1. MS, *m*/*z* 353 (M^+).
10. *Typical procedure [reaction of benzoxazole* (**1**) *with iodobenzene* (**2a**), *Table 1, entry 9]*: In a 20 mL two-necked flask were added **1** (119 mg, 1 mmol), **2a** (245 mg, 1.2 mmol), CuI (190 mg, 1 mmol), PPh_3 (52.4 mg, 0.2 mmol), Na_2CO_3 (212 mg, 2 mmol), 1-methylnaphthalene (ca. 50 mg, internal standard), and DMF (1 mL). The resulting mixture was stirred under N_2 (with balloon) for 2 h at 160 °C (bath temperature). After cooling, the mixture was poured into water containing ethylenediamine (ca. 2 mL), extracted with ether, and dried over sodium sulfate. Product **3a** was isolated by column chromatography on silica gel using hexane–ethyl acetate (99:1, v/v). The spectroscopic data were identical with those reported previously.[3a]